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The utility of peripheral blood leucocyte ratios as biomarkers in infectious diseases: A systematic review and meta-analysis

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SUMMARY

Objectives: To assess the utility of the neutrophil:lymphocyte (NLR), lymphocyte:monocyte (LMR) and platelet:lymphocyte ratios (PLR) as infection biomarkers.
Methods: PubMed/MEDLINE, Embase and Cochrane databases were searched to identify eligible articles. Studies of diagnosis, severity or outcome were included. PROSPERO systematic review registration CRD42017075032.
Results: Forty studies were included, reporting on bacterial and viral infections, malaria, and critical illness due to sepsis. Ten studies reported an association of higher NLR with bacteraemia, supported by meta-analysis of patient-level data (five studies, $n = 3320$; AUC 0.72, $p < 0.0001$) identifying a cut-off of >12.65. Two studies reported an association with lower LMR and diagnosis of influenza virus infection in patients with respiratory tract infection. Meta-analysis of patient-level data ($n = 85$; AUC 0.66, $p = 0.01$) identified a cut-off of ≤ 2.06. The directionality of associations between NLR and outcomes in heterogeneous cohorts of critically ill adults with sepsis varied. Potential clinical utility was also demonstrated in pneumonia (NLR), pertussis (NLR), urinary tract infection (NLR), diabetic foot infections (NLR) and Crimean Congo Haemorrhagic Fever (PLR). Longitudinal measurement of LMR during respiratory virus infection reflected symptoms and NLR during sepsis and bacteraemia predicted mortality.
Conclusions: Peripheral blood leucocyte ratios are useful infection biomarkers, with the most evidence related to diagnosis of bacteraemia and influenza virus infection. In critical illness due to sepsis, a signal towards an association with NLR and outcomes exists, and NLR should be evaluated in future stratification models. Longitudinal measurement of ratios during infection could be informative. Overall, these biomarkers warrant further recognition and study in infectious diseases.

Introduction

Infection biomarkers can be used as adjuncts to inform differential diagnosis (e.g. distinguishing bacterial from viral infection), as prognostic markers to stratify patients into sub-groups and endotypes,[1] and to monitor the response to antimicrobial therapy to guide duration. Canonical biomarkers include the total white cell count (WCC) and C-reactive protein (CRP). For over ten years there has been increasing interest in the use of procalcitonin as a biomarker for discrimination of bacterial from viral infection, and to assess response to antimicrobial therapy. Meta-analyses of clinical trials indicate that procalcitonin results can reduce antimicrobial usage and improve outcomes in respiratory tract infections with similar findings in critically ill patients with presumed

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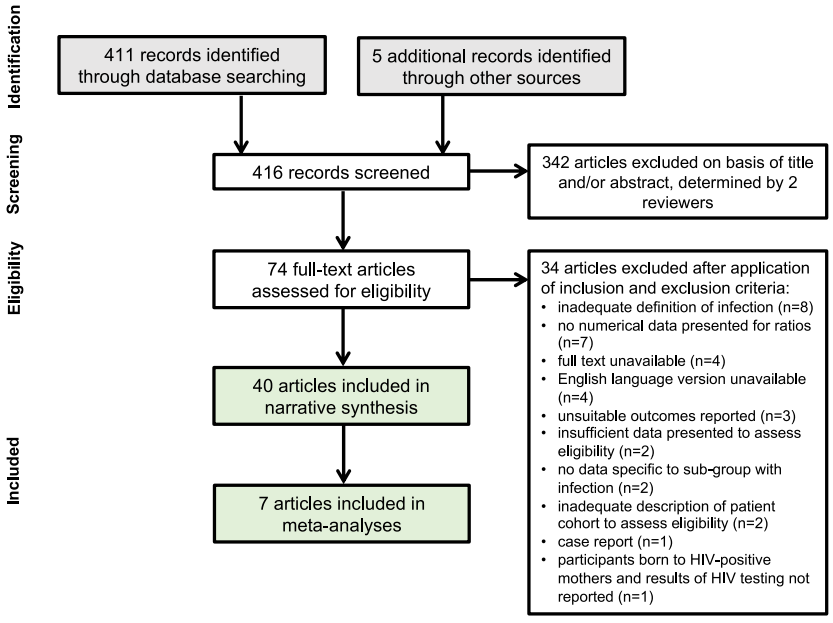

Fig. 1. PRISMA flow diagram illustrating article selection process.

bacterial sepsis in the intensive care unit (ICU).[2–4] However, procalcitonin measurement is currently expensive and is not universally available. In contrast, the full blood count is a cheap, fast and ubiquitous laboratory investigation. Automated counters provide a differential WCC, enumerating circulating leucocytes including neutrophils, lymphocytes and monocytes, but these parameters are usually interpreted in isolation.

During sepsis, apoptosis of B-cells and T-cells causes lymphocyte depletion, and peripheral blood lymphopenia is associated with mortality and nosocomial infection.[5–9] Lymphopenia is also associated with the presence of bacteraemia and can be a better predictor than neutrophil and total WCC.[10] Peripheral blood neutrophilia during sepsis, involving demargination and enhanced marrow recruitment, combined with systemic neutrophil activation, can contribute to inflammatory tissue damage and organ failure.[11] It is therefore biologically plausible that the neutrophil:lymphocyte ratio (NLR) and other leucocyte ratios could be informative biomarkers in patients with infection, reflecting underlying immune (dys)function, at least in peripheral blood. The ready availability and low cost of such indices would make them particularly helpful in low- and middle-income countries. In these settings, patient stratification to identify those requiring higher levels of care and discrimination of bacterial/non-bacterial infection to aid antimicrobial stewardship would be especially valuable.

This paper systematically reviews the literature evaluating the diagnostic and prognostic utility of the NLR and other peripheral blood leucocyte ratios (lymphocyte:monocyte and platelet:lymphocyte ratios; LMR and PLR respectively) in patients with infections. The PRISMA Statement has been followed in the conduct and reporting of this systematic review.[12]

Methods

Protocol and search

The protocol was registered with the PROSPERO international prospective register of systematic reviews (CRD42017075032, available at https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=75032). Briefly, the following key words were used to search the PubMed/MEDLINE, Embase and Cochrane databases on 25th June 2017: monocyte, lymphocyte, neutrophil, platelet, ratio, infection, sepsis, bacteraemia.

Eligibility criteria

We included observational studies and clinical trials where the ratios were measured in peripheral blood from humans of any age with viral, bacterial or parasitic infections. Case reports, conference abstracts and review articles were excluded. We accepted both clinical and microbiological diagnoses of infection, which had to be distinguished from evidence of systemic inflammation alone (e.g. elevated CRP or presence of systemic inflammatory response syndrome (SIRS) alone was insufficient). The type of infection had to be reported (syndrome, organ system involved or organism) and the ratio had to be quantified numerically. We included studies reporting the following data: diagnosis of infection (compared to healthy controls, non-infectious diagnosis or alternative infection); severity of infection (any measure) and outcome of infection (any measure). Due to possible confounding effects on the ratios, we excluded studies conducted exclusively in patients with active cancer, chronic liver disease (including HBV and HCV infection), HIV or immunosuppression. We excluded studies using non-routine laboratory techniques to quantify peripheral blood cell counts or diagnose infection. Specifically, investigative use of PCR for bacterial diagnosis was excluded. Individuals of any age were included and results presented refer to adults unless otherwise stated.

Study selection

All title/abstracts returned from the database search (Fig. 1) were reviewed by two authors (CDR and HJG) independently to assess the need for full text review. Full text articles were reviewed independently by the same two authors to assess eligibility. Reasons for exclusion were recorded.

Data collection and analysis

A data extraction proforma was constructed, iteratively modified, then used to extract data from included studies by two authors (CDR and AP). Risk of bias in patient selection and outcomes reporting was assessed (Supplementary Fig. 1). Synthesis of results

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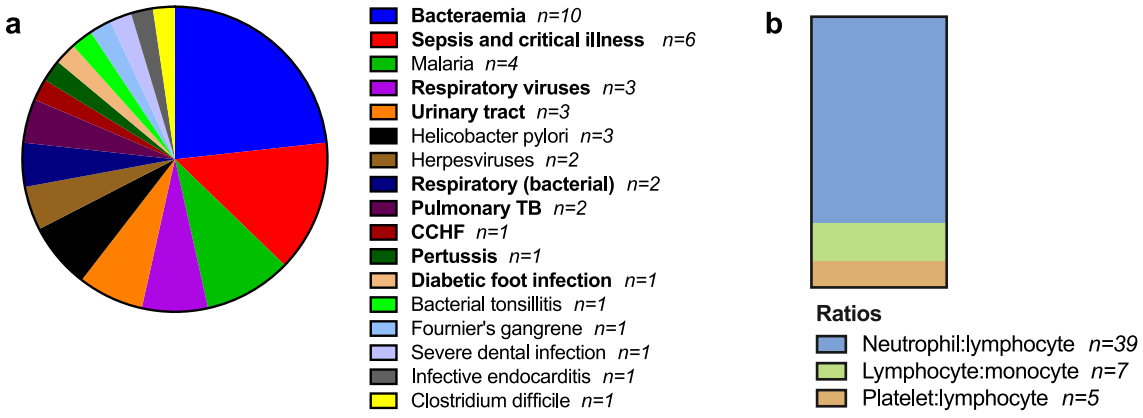

Fig. 2. Infectious diseases and leucocyte ratios reported. **a** Infectious diseases and **b** leucocyte ratios reported in 40 included studies. Note that some studies reported more than one ratio and bacteraemia was reported separately in some studies so is included as an additional category when relevant, therefore each total exceeds 40. The ratios investigated in patients with infectious diseases shown in bold were considered to demonstrate potential clinical utility. CCHF: Crimean Congo haemorrhagic fever.

was narrative with additional meta-analysis of patient-level data from relevant studies where provided by authors on request. Statistical analyses were performed using GraphPad Prism version 7.0.

Results

The infectious diseases and leucocyte ratios reported by the 40 included studies are shown in Fig. 2.

Sepsis and critical illness

Prognosis

The NLR was examined retrospectively in 1395 patients with severe sepsis (46%) or septic shock (54%), defined using 2001 criteria.[13,14] Patients were excluded if they had terminal malignancy, a previous "do not resuscitate" order or declined invasive procedures. The most common sites of infection were lung, intra-abdominal and urinary tract. Patients were initially stratified by NLR quintile (ascending from quintiles 1 through 5). The overall median initial NLR was 8.6 (0.2 in quintile 1, 31.0 in quintile 5). In higher quintiles, hypertension and diabetes were over-represented whereas metastatic solid cancers and haematological malignancies were under-represented. Multivariate analysis (including age, sex, initial SOFA score, co-morbidities, site of infection, requirement for mechanical ventilation, lactate and CRP) showed that an initial low (quintile 1, adjusted HR 1.79, 95% CI 1.15–2.78, $p=0.01$) or high (quintile 5, adjusted HR 1.67, 95% CI 1.04–2.66, $p=0.03$) NLR was associated with 28-day mortality when compared to quintile 3. The NLR trajectory over the first 48-h had greater prognostic value than initial measurement alone. Patients with persistently low (quintile 1, minimal/no change, adjusted HR 2.25, 95% CI 1.63–3.11, $p<0.01$) or high (quintile 5, minimal/no change, adjusted HR 2.65, 95% CI 1.64–4.29, $p<0.01$) NLR were at higher risk of 28-day mortality.

A prospective study investigated NLR in 333 patients with sepsis in the ICU (2001 criteria; septic shock in 14% [14]).[15] The most common sites of infection were lung, intra-abdominal and urinary tract. Baseline NLR (within 24-h of admission) was higher in non-survivors at 28-days ($n=80$, median 25.5) compared to survivors ($n=253$, 15.0; $p<0.001$). In ROC analysis the NLR had an AUC for predicting 28-day mortality of 0.70 (±0.04), compared to 0.83 (±0.03) for baseline APACHE II score. The NLR positively correlated with the APACHE II score at baseline ($r=0.64$, $p<0.001$). In multivariate analysis (including age and APACHE II), APACHE II score was most predictive of 28-day mortality (OR 1.17, 95% CI 1.11–1.23) but NLR remained a significant co-variate (OR 1.04, 95% CI 1.01–1.08).

A prospective study of 130 patients with septic shock (2001 criteria[14]) examined the NLR as a predictor of ICU mortality, including stratification into early (day 1–4) and late death (≥day 5).[16] Intra-abdominal infection accounted for 75% of cases. The NLR at admission was higher in survivors ($n=76$, median 12.5) compared to non-survivors ($n=54$, median 6.2, $p=0.0014$). The NLR was not significantly different between early ($n=33$) and late ($n=21$) deaths. The NLR trajectory, when measured daily on days 1–5, was evaluated in the late death group compared to survivors. Admission NLR was higher in the survivors (median 11.8 vs. 7.0, $p=0.06$) but this was reversed at day 5, where the NLR was lower in survivors (median 9.1 vs. 12.8, $p=0.028$). The trajectory over days 1–5 showed a significant difference: −20% in survivors compare to +35% in the late death group ($p=0.003$).

In a retrospective study of 5056 un-selected ICU patients, NLR on ICU-admission was compared in patients with ($n=1832$) and without ($n=3224$) sepsis (2001 criteria[14]).[17] Patients with sepsis had higher baseline NLR (median 10.9 vs. 8.1, $p<0.001$).

Other outcomes

A retrospective study of 118 patients with severe sepsis (2001 criteria[14]) demonstrated an association between a higher NLR on ICU admission and subsequent development of acute kidney injury (AKI; defined as creatinine ≥0.3 mg/dL from baseline, ≥50% increase in creatinine or urine output of <0.5 mL/kg/h for >6 h).[18] The mean NLR was 13.6 in patients with AKI compared to 7.8 in patients without ($p<0.001$). NLR remained an independent co-variate in multi-variate analysis (including age, APACHE II, use of ACE inhibitor or angiotensin receptor blocker, duration of mechanical ventilation and SOFA score; OR for AKI 3.25, 95% CI 2.72–4.19, $p<0.001$).

A higher admission NLR and PLR were associated with nosocomial infection (clinician diagnosed; $n=42/173$; mean NLR 18.1 vs 11.2, $p=0.002$; PLR 323 vs 229, $p=0.009$) in a retrospective report of un-selected ICU patients.[19]

Bacteraemia

Prognosis

A retrospective cohort of 2311 patients with bacteraemia/fungaemia reported on the utility of sequential NLR measurement as a marker of 28-day mortality.[20] Patients with haematological malignancy, HIV and parasitic infection were excluded. *Escherichia coli* and other Gram negative bacteria were most commonly identified ($n=1298$) and fungaemia was uncommon ($n=29$). The NLR was higher in non-survivors on days 0–15 ($p<0.01$ each day), and this became more apparent from day 3 onwards. In multivariate analysis (including age, sex, Charlson co-morbidity index, infection site, microbiology results and

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Table 1
Summary of NLR, PLR and LMR as biomarkers of diagnosis or prognosis in infectious diseases.

Infection or syndrome	Ratio	Outcomes reported	Key findings	Potential clinical utility as biomarker	References
Critical illness and sepsis	NLR	28-day and ICU mortality Acute kidney injury Nosocomial infection Diagnosis of bacteraemia	Directionality of association between NLR and outcomes varied, likely related to heterogeneity within phenotypes of patients included (see text). Longitudinal measurement to identify trajectory of NLR predictive of survival.	Yes	13, 15, 16, 17, 18, 19
Bacteraemia	NLR	Diagnosis of bacteraemia 28-day mortality	Higher NLR associated with presence of bacteraemia in 10 studies (see Table 2 and Fig. 2).	Yes	13, 15, 16, 21, 22, 23, 24, 25, 26, 27
Bacterial infection					
Respiratory tract infection	NLR and PLR	Diagnosis of LRTI vs acute-on-chronic heart failure	Higher NLR associated with diagnosis of LRTI in patients with chronic heart failure presenting with dyspnoea of unclear aetiology.	Yes	37
Community acquired pneumonia	NLR	Infection severity *S. pneumoniae* infection Diagnosis of bacteraemia	Higher NLR associated with more severe infection, pneumococcal infection and diagnosis of bacteraemia.	Yes	21
Urinary tract infection	NLR	Presence of pyelonephritis in children with febrile UTI	Higher NLR predictive of pyelonephritis diagnosed by cortical defect on DMSA scan.	Yes	41, 42
Severe dental infection	NLR	Duration of hospitalisation Total doses antimicrobials	Higher NLR associated with worse outcomes	No; clinically uninformative outcomes presented	44
Diabetic foot infection	NLR	Presence of osteomyelitis Requirement for amputation	Higher NLR associated with outcomes	Yes	45
Bacterial tonsillitis	NLR	Presence of deep neck space infection (DNSI)	Higher NLR associated with DNSI	Unclear; clinical presentation of tonsillitis and DNSI significantly different without requirement for biomarker	46
Fournier's gangrene	NLR and PLR	Requirement for multiple debridements	Higher NLR and PLR associated with outcome	No; clinically uninformative outcome presented	47
Infective endocarditis	NLR	Composite of in-hospital mortality or CNS event	Higher NLR associated with worse outcome	No; clinically uninformative outcome presented	50
C. difficile infection	NLR and LMR	Diagnosis of CDI vs healthy controls	Lower LMR and higher NLR associated with CDI	No; comparison with healthy controls uninformative	51
H. pylori gastritis/peptic ulcer disease	NLR and PLR	Diagnosis of infection vs controls Symptomatic vs asymptomatic infection	Higher NLR and LMR associated with outcomes	No; biomarker not required and numerical differences not clinically significant	52, 53, 54
Pulmonary tuberculosis	NLR	Diagnosis of Mtb vs bacterial CAP	Lower NLR associated with Mtb in intermediate TB burden country	Yes	38
Pertussis	NLR	Infection severity (malignant pertussis)	Higher admission NLR associated with malignant pertussis.	Yes	40
Viral infection					
CCHF	PLR	Requirement for blood product transfusion In-hospital mortality	Lower PLR associated with need for transfusion of blood products and mortality.	Yes; prediction of transfusion requirements helpful.	28
Herpesviruses (BP and RHS)	NLR	Recovery Case vs healthy control	Higher NLR associated with worse outcome in Bell's palsy.	No; new biomarker for prognostication not required.	30, 33
Respiratory viruses	LMR	Symptom severity Diagnosis of viral vs. bacterial infection Diagnosis of influenza virus amongst patients with ILI	Lower LMR associated with symptom severity in respiratory virus infection, discrimination of influenza from pneumococcal pneumonia and confirmed influenza amongst patients with ILI.	Yes	34, 35, 36
Malaria	NLR and MLR	Diagnosis of malaria vs dengue	Differences observed but total WCC remained more discriminatory.	No; total WCC remains more useful than ratios whilst awaiting blood film or rapid diagnostic test results.	55, 56, 58, 59
		Diagnosis of *P. falciparum* vs *P. vivax*	Observed differences too small to be clinically significant.		
		Malaria severity	Conflicting data on association of higher NLR with complicated malaria.		

LRTI: lower respiratory tract infection; CDI: *C. difficile* infection; Mtb: *Mycobacterium tuberculosis*; BP: Bell's palsy; RHS: Ramsay Hunt syndrome; ILI: influenza-like illness; CAP: community-acquired pneumoniae.

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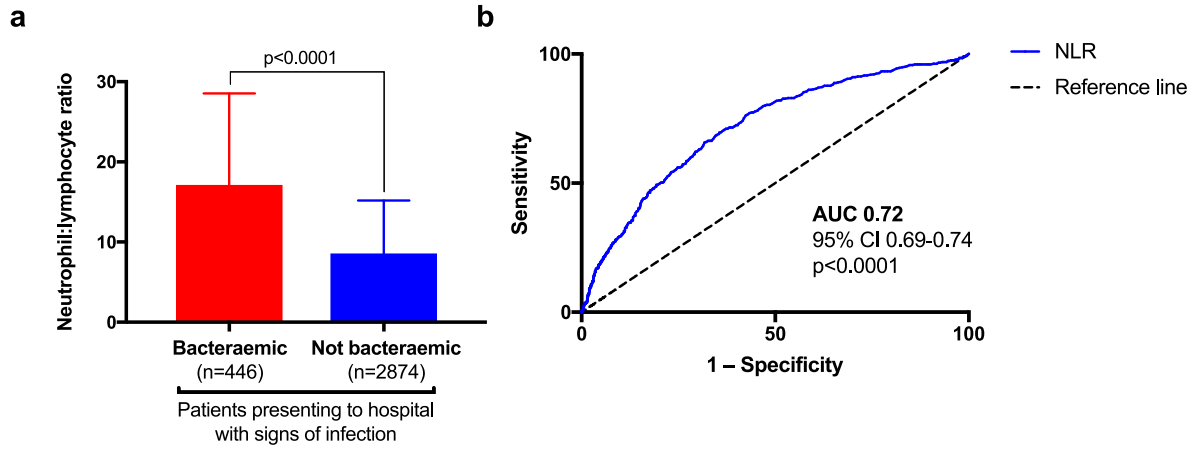

Fig. 3. Meta-analysis results for NLR and bacteraemia. **a** NLR median and interquartile range derived from meta-analysis of patient-level data for 3320 patients. **b** Receiver operator characteristic analysis for NLR in predicting presence of bacteraemia in these patients.

vasopressor-requirement), a NLR >7 was associated with mortality (HR 1.72, 95% CI 1.24–2.39).

Diagnosis

In addition to three studies providing data on the association between NLR and presence of bacteraemia in critically ill patients with sepsis and one in patients with CAP,[13,15,16,21] a further six report on this association in additional cohorts (Table 2). One study includes patients with sepsis outwith the ICU[22] and five include patients presenting to hospital with signs/symptoms suggestive of infection.[23–27] Across all of these studies, a consistent association with higher NLR and the presence of bacteraemia is reported. A meta-analysis of patient level data was performed using data provided by authors of five studies relating to 3320 patients presenting to the ED with signs of infection (Table 2, note only studies where authors provided patient level data were included).[21,23,25–27] The median NLR in patients with bacteraemia was 17.2 (interquartile range 10.2–28.4) compared to 8.6 (4.9–15.2) in patients without ($p<0.0001$). The ROC AUC was 0.72 (95% CI 0.69–0.74; Fig. 3). The optimum NLR cut-off was determined by Youden's J statistic as >12.65 (sensitivity 66%, specificity 68%, $J=0.34$). This cut-off provided an odds ratio of 4.1 (95% CI 3.3–5.1, $p<0.0001$) for bacteraemia.

Viral infections

Crimean Congo Haemorrhagic Fever (CCHF)

The PLR was evaluated in a cohort of 149 patients in Turkey with PCR-confirmed CCHF with an overall mortality of 7%.[28] Patients with PLR <41 ($n=38$) were more likely to require transfusion of blood products (25/38 vs 33/111, $p<0.001$) and had higher mortality (7/38 vs. 4/111, $p<0.001$). Use of previously reported independent predictors of mortality (thrombocytopenia, prolonged APTT, melaena and somnolence[29]) also performed well in identifying patients at risk of mortality, though the two were not compared directly. Patients receiving ribavirin were excluded, limiting the generalisability of these results.

Herpesviruses

The pre-treatment NLR was retrospectively investigated in predicting prognosis of Bell's Palsy (BP, $n=374$) or Ramsay Hunt Syndrome (RHS, $n=94$).[30] BP is most often due to herpes simplex virus re-activation but can also be caused by varicella zoster virus (VZV).[31] RHS is caused by VZV. Diagnoses were based on clinical findings and acute/convalescent serology. A higher baseline NLR was observed in patients without facial nerve recovery following BP at 6-months (mean 4.2 vs. 2.3, $p=0.0003$). Electroneurography and Yanagihara score (severity score to predict recovery[32]) were also associated. No association was observed in RHS.

The NLR was also reported retrospectively in 54 patients with BP and 45 healthy controls.[33] Cases were classified by the House–Brackmann scale pre- and post-treatment with corticosteroids (grade 1 is normal; grade 5 is complete paralysis). A higher NLR was observed in cases compared to controls (mean 2.7 vs 1.8, $p=0.001$) and was associated with poorer recovery (mean 3.4 for House–Brackmann score >2 vs 2.5 for score of 1 or 2, $p<0.05$).

Respiratory viruses including influenza virus

The LMR was measured daily in patients experimentally infected with influenza H3N2 ($n=17$), respiratory syncytial virus (RSV, $n=20$), and human rhinovirus (HRV, $n=20$).[34] Experimental infection resulted in symptoms and cell culture/PCR confirmed shedding in ~50% of cases. For all three viruses, symptomatic patients demonstrated a decrease in LMR with respect to asymptomatic patients and the trajectory of the LMR decline then recovery mirrored symptom severity. LMR <2 predicted 100% of all symptomatic influenza-infected patients at the time of maximal symptoms (day 3) and was less predictive of symptomatic RSV (60%) or HRV (18%). A comparative assessment of LMR in patients in the ED (not requiring hospitalisation) diagnosed with PCR-confirmed H1N1 influenza ($n=18$) or culture-proven *Streptococcus pneumoniae* community-acquired pneumonia (CAP; $n=18$) found LMR <2 was associated with influenza (67% vs 38%, $p=0.05$).

Finally, the LMR was evaluated in a cohort of patients with influenza-like illness (ILI, $n=37$) due to PCR-confirmed human metapneumovirus, coronaviruses, HRV, human parainfluenza virus 3 (HPIV-3) or RSV.[35] LMR <2 was found more often in patients with HPIV-3 compared to the other viruses. In another cohort of patients with ILI presenting to the ED ($n=58$), LMR <2 was observed more commonly in patients with a positive influenza antigen test (85% vs 67% for all patients).[36] 48% of patients with LMR <2 had a positive antigen test.

A meta-analysis of patient level data was performed using data provided by authors of two studies relating to 85 patients with symptomatic respiratory tract infection.[34,36] The median LMR in patients with influenza virus infection was 1.5 (interquartile range 1.1–2.0) compared to 2.1 (1.3–3.1) in patients without ($p=0.01$). The ROC AUC was 0.66 (95% CI 0.55–0.78; Fig. 4). The optimum LMR cut-off was determined by Youden's J statistic as ≤2.06 (sensitivity 54%, specificity 80%, $J=0.34$). This cut-off provided an odds ratio of 4.7 (95% CI 1.8–12.6, $p=0.001$) for influenza virus infection.

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Table 2
Neutrophil:lymphocyte ratio in patients with bacteraemia.

Setting	Study design	Population	Bacteraemia identified	Microbiology results (blood cultures)[a]	Neutrophil:lymphocyte ratio (NLR)			ROC analysis AUC (95% CI)		Inclusion in meta-analysis	Ref
					Bacteraemia	Comparison group[b]	*p*-value	Bacteraemia	Comparator parameters		
ICU	Retrospective cohort	Severe sepsis or septic shock	609/1395	Not reported	5th NLR quintile (median NLR 31.0) 52%	Entire cohort (median NLR 8.6) 44%	<0.01	Not presented		No: data not provided	13
	Prospective cohort	Sepsis	112/333	Gram negative most common, predominantly *E. coli*	Median NLR 22.7	Median NLR 14.7	<0.001	Not presented		No: data not provided	15
	Prospective cohort	Septic shock	22/130	GNB 47%, GPC 34%	Median NLR 13.9	Median NLR 8.8	0.024	Not presented		No: data not provided	16
Inpatient	Retrospective cohort	Sepsis	60/120	Not reported	Median NLR 16.9	Median NLR 8.4	<0.001	0.72 (0.62–0.81)	CRP 0.67 (0.57–0.76) PCT 0.83 (0.75–0.91)	No: data not provided	22
ED	Prospective cohort	Suspected infection	76/1083	Not reported	Mean NLR 17	Mean NLR 8	<0.001	0.70	CRP 0.65 WCC 0.54	Yes	23
	Retrospective cohort	Fever	270/1954	*E. coli* ($n=78$) > Streptococci and Staphylococci	Median NLR 16.0	Median NLR 8.6	<0.001	0.71 (0.69–0.75)	Lymphocytes 0.71 (0.68–0.74) CRP 0.66 (0.63–0.70) WCC 0.53 (0.49–0.57)	No: data not provided	24
	Retrospective cohort	Suspected infection and ≥2 SIRS criteria	20/125	*E. coli* ($n=10$) Other GNB ($n=5$) *S. aureus* (n = 1) *S. gallolyticus* ($n=1$) *S. pneumoniae* ($n=1$) Viridans group Streptococcus ($n=1$) *C. paraputrificum* ($n=1$)	Mean NLR 23.0	Mean NLR 12.2	<0.001	0.77	CRP 0.49 PCT 0.81	Yes	25
	Retrospective cohort	Suspected bacteraemia[c]	92/746 (100 bacterial isolates)	Gram negative ($n=61$; of which *E. coli* $n=45$) Gram positive ($n=39$, of which *S. pneumoniae* $n=15$).	Mean NLR 20.9	Mean NLR 13.2	<0.0001	0.73 (0.66–0.81)	CRP 0.62 (0.54–0.70) WCC 0.53 (0.44–0.61) Neutrophils 0.57 (0.49–0.66) Lymphocytes 0.73 (0.66–0.80)	Yes	26
	Prospective cohort	Suspected infection	197/1572	Not reported	Median NLR 16.6	Median NLR 8.8	<0.01	0.71, (0.67–0.75)	PCT 0.74 (0.70–0.78) CRP 0.56 (0.51–0.60) Lactate 0.66 (0.61–0.70)	Yes	27
	Prospective cohort	CAP	42/395	Not reported	Mean NLR 22.5	Mean NLR 12.6	<0.01	Not presented		Yes	21

[a] Microbiology results are presented in as much detail as could be extracted from publication.
[b] Unless otherwise stated the comparison group was the remainder of the cohort without bacteraemia.
[c] Criteria not reported. ICU: intensive care unit; ED: emergency department; GNB: Gram negative bacillus; GPC: Gram positive coccus; CAP: community-acquired pneumonia; PCT: procalcitonin.

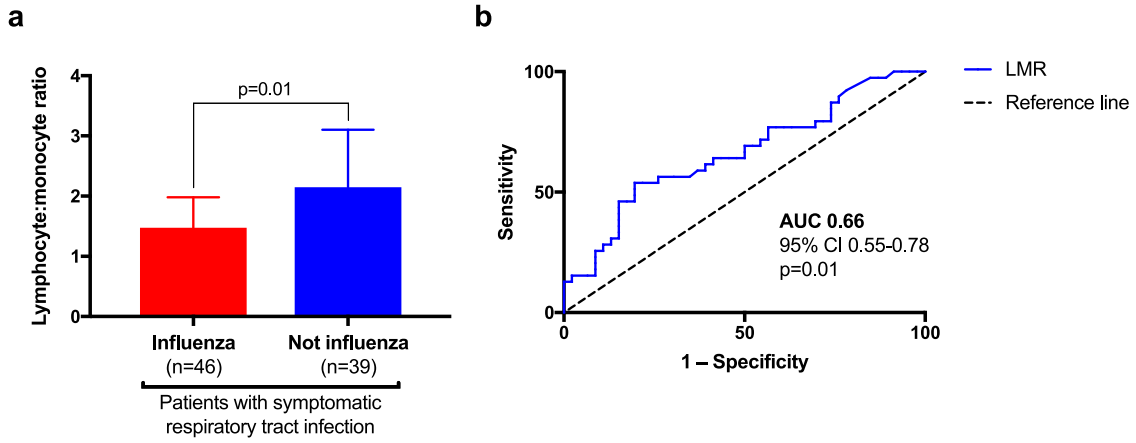

Fig. 4. Meta-analysis results for LMR and influenza virus infection. **a** LMR median and interquartile range derived from meta-analysis of patient-level data for 85 patients. **b** Receiver operator characteristic analysis for LMR in predicting presence of influenza virus infection in patients with symptomatic respiratory tract infection.

Bacterial infections

Respiratory tract infections

The utility of NLR and PLR in differentiating acute heart failure (AHF) from respiratory tract infection (RTI) was investigated retrospectively in patients with chronic heart failure (CHF) who were hospitalised due to dyspnoea.[37] Patients were excluded if a diagnosis of RTI could be made confidently or if they were immunosuppressed. The NLR was higher in patients with a final diagnosis of RTI (6.2 vs 3.1, $p<0.01$) and total WCC was not.

The NLR measured in the ED was studied prospectively in 395 patients with radiologically-confirmed CAP.[21] The NLR progressively increased amongst sub-groups of patients with increasing infection severity (overall mean NLR 13.6, hospital admission [$n=346$] 14.4, ICU admission [$n=31$] 18.7, in-hospital mortality [$n=23$] 23.3). The NLR also sequentially increased with each increment in CURB-65 score. A NLR cut-off of ≥ 10 was associated ($p<0.01$) with co-morbid COPD (65%), bacteraemia (79%), *S. pneumoniae* infection (89%), ICU admission (74%) and in-hospital mortality (78%). NLR <10 was associated with *Coxiella burnetii* infection (78%, $p<0.01$) with more infections than expected with this pathogen (16% of infections, compared to 18% *S. pneumoniae*) due to a Q fever epidemic during the study period. ROC analysis for mortality showed the NLR (AUC 0.70) to be superior to neutrophil count (AUC 0.68, lymphocyte count (0.63), total WCC (0.67) and CRP (0.57). The NLR was not independently associated with outcome when included in multivariate analysis with age and co-morbidities.

Pulmonary tuberculosis

A Korean study compared NLR in patients with bacterial CAP ($n=94$) and *Mycobacterium tuberculosis* pulmonary infection ($n=112$) in a setting of intermediate TB burden.[38] CAP was diagnosed on the basis of clinical findings, resolution of chest x-ray infiltrate after antimicrobials, negative sputum/lavage fluid culture for *M. tuberculosis*, and negative viral PCR. It is not clear if mycobacterial cultures were performed on all respiratory specimens. Pulmonary TB was diagnosed based on positive sputum/lavage culture or adenosine deaminase concentration in pleural fluid combined with compatible parenchymal lesions. A mean NLR of 14.6 was observed in CAP, compared to 3.7 in TB ($p<0.001$). When a cut off of <7.0 was used, the sensitivity of NLR was 91% and specificity was 82% for predicting TB. In ROC analysis the NLR performed better than CRP (NLR AUC 0.93, 95% CI 0.88–0.96; CRP AUC 0.83, 95% CI 0.76–0.88). Patients who had received antimicrobials for >24-h at admission were excluded (135/424 screened patients), limiting the generalisability of these results.

NLR was assessed retrospectively in patients with acid-fast bacilli- or culture-positive pulmonary tuberculosis ($n=51$), biopsy-confirmed sarcoidosis ($n=40$), and healthy controls ($n=43$).[39] Patients receiving corticosteroids were excluded. NLR was higher in the TB (mean 5.6) cohort compared to the sarcoidosis (mean 2.5) and control (mean 1.7) cohorts ($p<0.001$).

Pertussis

Admission NLR was studied retrospectively in 152 children with *Bordetella pertussis,* confirmed microbiologically in 151 cases.[40] Malignant pertussis (11/152) was diagnosed based on presence of pneumonia, pulmonary hypertension or vasopressor-requirement. NLR was higher in patients with malignant compared to benign pertussis (median 1.1 vs 0.3, $p=0.001$). NLR predicted malignant pertussis with an AUC of 0.96 in a multivariate model including NLR >1.0, total WCC $>25\times10^9$ cells/L, and heart rate >180 beats/minute. The adjusted odds ratio within this model for NLR >1.0 was 30.7 (95% CI 3.7–255) compared to 15.6 (95% CI 1.8–135) for total WCC.

Urinary tract infection (UTI)

The utility of the NLR in predicting DMSA scan cortical lesions (indicative of pyelonephritis) was investigated retrospectively in 133 children (0–10 years) with first episode of febrile, microbiologically-confirmed UTI.[41] All patients with prior UTI or urogenital abnormalities other than vesico-ureteric reflux (VUR) were excluded. NLR was higher in patients with a cortical lesion on initial DMSA and was a significant co-variate (OR 1.6, $p=0.007$) following logistic regression including age, sex, VUR, WCC and CRP. In a similar study of children <36 months with first episode of microbiologically-confirmed febrile UTI ($n=298$) who were evaluated by DMSA, the NLR was higher in patients with a cortical defect (mean 2.5 vs 1.4, $p<0.001$).[42]

Pre-operative NLR as a predictor of post-operative sepsis was assessed retrospectively in 487 patients undergoing percutaneous nephrolithotomy.[43] 5% of patients developed post-operative infection, with the organism most commonly detected on stone culture being *E. coli* (47%). Patients with NLR >2.5 had a higher incidence of postoperative infection ($p=0.006$). Pre- and post-operative urine culture positivity were both associated with higher NLR ($p=0.039$ and 0.003, respectively).

Soft tissue and bone infection

In 100 patients with severe dental infection (mostly submandibular abscess) requiring surgical intervention, an association

was reported between NLR and both duration of hospitalisation (median 3.7 for ≤1 day vs. 5.3 for >1 day, $p=0.027$) and total doses of antimicrobials received (correlation, $p<0.01$).[44]

The association between NLR and outcome of diabetic foot infection was examined in a cohort of 75 patients, managed with amputation ($n=25$), debridement/drainage ($n=25$) or no surgical intervention ($n=25$).[45] The NLR was higher in patients who required amputation (mean 15.7, $p=0.001$), compared to those requiring debridement (9.9) or no intervention (6.0). The NLR was higher in patients who went on to develop osteomyelitis (mean 12.3 vs 6.0, $p=0.004$). Similar associations were observed between outcomes and erythrocyte sedimentation rate.

A cohort study examined the predictive value of NLR for radiologically-confirmed deep neck space infection (DNSI) in children (6 months-17 years) with bacterial tonsillitis.[46] Patients with uncomplicated bacterial tonsillitis ($n=156$) had a lower NLR than patients with DNSI ($n=24$; median NLR 1.5 vs 12.8, $p<0.01$).

NLR and PLR were examined retrospectively in patients with Fournier's gangrene.[47] Fournier's gangrene was diagnosed clinically, with all patients having Fournier Gangrene Severity Index (FGSI) scores calculated on admission (comprising temperature, heart rate, respiratory rate, serum sodium, serum potassium, serum creatinine, serum bicarbonate, haematocrit and total WCC[48]). Patients were divided into those who underwent a single debridement ($n=27$) compared to those who underwent multiple debridements ($n=41$). Patients undergoing a single debridement had a lower NLR (7.7 vs 14.5, $p<0.001$) and PLR (182 vs 304, $p<0.001$). The initial mean FGSI did not differ between groups.

Infective endocarditis

In a case control study of patients with infective endocarditis diagnosed using the modified Duke Criteria,[49] NLR was examined as a predictor of adverse in-hospital outcomes.[50] These were defined as in-hospital mortality or an intra-cerebral event (cerebrovascular event, meningitis, embolism, or brain haemorrhage). The NLR was higher in patients who had a negative outcome ($n=46$; mean 11.4) compared to those who did not ($n=75$; mean 4.8, $p<0.001$). This association was significant ($p<0.001$) in a multivariate analysis including other predictors of adverse outcomes (including *Staphylococcus aureus* infection, end stage renal disease and requirement for surgery) with a hazard ratio for NLR of 1.4 (95% CI 1.3–1.48). ROC analysis showed the NLR to be a better predictor of adverse outcomes compared to CRP or total WCC (AUC for NLR 0.82, 95% CI 0.75–0.90; CRP 0.76, 95% CI 0.67–0.85; and WCC 0.67, 95% CI 0.56–0.78).

Clostridioides difficile infection

The NLR and LMR were evaluated in a case-control study for differentiation of active ulcerative colitis (UC) from UC in remission and from *C. difficile* infection ($n=75$; diagnosed by detection of toxin A or B by PCR in stool and with no history of inflammatory bowel disease) and healthy controls without gastrointestinal disease ($n=75$).[51] Although the authors' analysis aimed to describe these ratios in the context of UC, sufficient data were presented to compare *C. difficile* infection with the healthy controls. The LMR was lower in *C. difficile* infection compared to healthy controls (mean 1.5 vs 3.5) and the NLR was higher (mean 7.0 vs 2.6).

Helicobacter pylori infection

Three studies reported on the PLR and NLR in the evaluation of *Helicobacter pylori* infection. The PLR was incrementally higher in patients with symptomatic *H. pylori* (mean 155, $n=100$), asymptomatic *H. pylori* (115, $n=100$) and healthy controls (108, $n=108$; $p<0.001$).[52] Infection was diagnosed by urea breath testing then confirmed by gastric biopsy. In a similar study using the same diagnostic criteria, the NLR was higher in patients with *H. pylori* infection ($n=50$) compared to patients with gastritis of other aetiologies ($n=50$) (5.1 vs 2.9, $p<0.001$).[53] Two weeks after successful therapy (resolution of symptoms and negative urea breath test) the NLR had normalised. However, it is not clear if therapy was unsuccessful in any cases and if so, the trajectory of the NLR in such cases. Finally, the NLR was higher in patients with endoscopically and urease confirmed *H. pylori* peptic ulceration ($n=60$, mean 1.7) compared to healthy controls ($n=32$, mean 1.2; $p<0.001$).[54]

Malaria

The NLR and MLR were retrospectively evaluated for differentiation of malaria and dengue (detection of NS1 antigen or IgG/M antibody) in 683 patients in Thailand.[55] *P. vivax* infection was more common (73%) than *P. falciparum* (21%) in this cohort. In comparison to dengue, the median NLR and MLR were higher in malaria (NLR 3.9 vs 1.2, $p<0.0001$; MLR 0.27 vs 0.17, $p<0.0001$). Neither NLR or MLR were significant co-variates in a multivariate analysis including age, gender, nationality and other haematological parameters, but the total WCC and neutrophil count remained significantly different (lower in dengue). The NLR and MLR were reported in 4985 patients with *P. falciparum* (50%) and *P. vivax* (50%) malaria in Thailand, finding a median NLR of 2.8 in falciparum, 2.7 in vivax, and 2.2 in non-infected controls ($p<0.0001$).[56] This study also reported a MLR of 0.30 in falciparum, 0.29 in vivax, and 0.24 in controls ($p<0.0001$).

In 440 cases of imported malaria in the Netherlands, no significant variation in NLR between severe falciparum per WHO guidelines[57] (median 3.5), non-severe falciparum (median 3.3) or non-falciparum (median 2.8) was observed.[58] The degree of parasitaemia did correlate with NLR ($p=0.03$). In another cohort of imported malaria in Munich ($n=210$) the NLR was higher in complicated vs. uncomplicated cases (median 3.6 vs 2.2, $p=0.12$) and the MLR did not differ (median 0.25 vs 0.28, $p=0.63$).[59]

Discussion

Summary of evidence

Peripheral blood leucocyte ratios have been investigated in the context of bacterial infections (including bacteraemia), viral infections, malaria and critical illness due to sepsis. The most consistent association reported by ten studies is an association with higher NLR and the presence of bacteraemia, supported by meta-analysis of data provided from five of these studies (Table 2 and Fig. 3). An explanation for the consistency of this association may be that the NLR is being measured in the same compartment as the infection.

NLR was found to be associated with outcome measures in six studies of critically ill adults with sepsis, but the directionality of the association was not consistent and this is likely due to heterogeneity at several levels. Microbial aetiology and site of infection notwithstanding, there is significant variation in the host response to infection represented in the cohorts, with septic shock accounting for between 14% and 100% of cases. Furthermore, analysis strategies differ between studies with the use of quintiles in one study compared to continuous variables in the others. Quintiles allow better differentiation of outlier values from normal and thus may be more discriminatory. It is interesting that amongst patients with sepsis, of whom 54% were diagnosed with septic shock,[13] a high NLR was associated with mortality whereas in a cohort composed only of patients with septic shock the reverse was observed.[16] Previous work has demonstrated more lymphocyte apoptosis in patients with septic shock compared to sepsis without shock, and this lymphocyte depletion was associated with poorer

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outcomes.[9] Whilst this paradigm is consistent with some of the observations that have been reported, an apparent paradox exists where some studies report the converse.[13,16] Neutrophil depletion is one possible contributing factor but this warrants further investigation and highlights the importance of high-throughput clinical phenotyping.[1] Sepsis syndrome includes a wide range of infectious aetiologies and heterogeneous host responses. Given the evidence we report here, and the ubiquity of full blood count data, it is likely that NLR will be a more informative parameter (compared to total WCC, neutrophil count and CRP) to include in future stratification models to identify sepsis endotypes.[1]

Potential clinical utility of the ratios was also demonstrated in patients with respiratory tract infections, febrile UTI in children, diabetic foot infections, respiratory virus infections and CCHF (Table 1), though prospective validation is required in all cases. Considering respiratory virus infection, two studies reported an association with lower LMR and influenza virus infection amongst adults with respiratory tract infection (meta-analysis, Fig. 4).

The ratios were investigated in a number of cohorts where the clinical utility of the identified associations was unclear and, in our opinion, there is no urgent need for new biomarkers, for example *H. pylori* gastritis, distinguishing pulmonary TB from sarcoidosis and predicting outcome in Bell's palsy (Table 1). Although differences in NLR and MLR were identified between malaria and dengue, we found no evidence for clinical utility since the total white cell count remained a better discriminator, rapid diagnostic tests exist for both organisms, and the absolute differences in the ratios were too small to be clinically significant. Finally, several studies used outcome measures lacking true clinical relevance, such as duration of hospitalisation in severe dental infection, requirement for >1 debridement in Fournier's gangrene and a composite measure of in-hospital mortality and CNS events in endocarditis.

During experimental infection following human challenge with respiratory viruses, the LMR trajectory mirrored symptom severity. In a cohort of patients with severe sepsis or septic shock, the NLR trajectory over the first 48-h (persistently low or persistently high) was a better predictor of 28-day mortality than initial measurement in isolation. Finally, in patients with bacteraemia a higher daily NLR from day 3 onwards predicted 28-day mortality. Therefore, longitudinal measurement during the course of infection is likely to be informative and normalisation could signal recovery and thus contribute to decision-making around antimicrobial duration.

Limitations

Bias at the levels of patient selection and outcome reporting is shown in Supplementary Table 1. Findings in the majority of studies have not been replicated or validated in prospective studies. The peripheral blood lymphocyte count can be higher in young children, and this should be considered when interpreting the results of the studies conducted in children (pertussis[40] and UTI[41,42]). Finally, some studies compare healthy with infected individuals and this is less useful than stratifying within an infection syndrome.

Conclusions

Overall, we have identified a consistently reported association between the NLR and presence of bacteraemia and this is clinically relevant in the interpretation of routine clinical data in circumstances where the presence or absence of bacteraemia is the relevant clinical question, prior to results from blood cultures. Results from studies in critically ill adults with sepsis suggests a signal towards outcome may exist, but more sophisticated patient stratification and data analysis will be required to determine any utility in identifying sepsis endotypes. Longitudinal measurement during the course of infection could be informative but this hypothesis requires testing. The ability to identify influenza virus infection in patients with respiratory tract infection using LMR is potentially useful if validated, and more generally the investigation of these ratios in the discrimination of bacterial/viral/parasitic aetiologies would be valuable. Future work should focus on patient cohorts in need of new biomarkers and avoid comparisons of infected and healthy individuals. Overall, these biomarkers warrant further recognition and study in infectious diseases.

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Conflict of interest

None.

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Supplementary material

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